147 Anemia

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Definition

Anemia is defined as a decrease in the red blood cell mass. Accurate measurements require labeling of erythrocytes followed by in vivo quantification of the dilution of the labeled cells in the circulation. Obviously, this is an impractical method for the detection of anemia, and measurements of either the hemoglobin concentration, the hematocrit, or red blood cell count are used. Each of these latter methods is complicated by the fact that they represent concentrations that can be altered by variations in the plasma volume without changes in the red blood cell mass. Usually this is usually not important in the clinical setting for the detection of anemia, but it should be considered by the physician.

The World Health Organization has decided that anemia exists in adults whose hemoglobin values are lower than 13 g/dl in males and 12 g/dl in females. Children age 6 months to 6 years are considered anemic at hemoglobin levels below 11 g/dl; and between 6 and 14 years, below 12 g/dl. The disadvantage of these arbitrary criteria is that they include some normal individuals who fall below the defined value. In the United States, slightly higher values are usually cited, and males with a hemoglobin below 13.5 g/dl and females with a hemoglobin below 12.5 g/dl probably should be considered anemic. Higher values are anticipated in individuals living at altitudes significantly above sea level. In conditions in which there is an increase in the plasma volume, such as the last trimester of pregnancy, lower hemoglobin values will be encountered even though the red cell mass is normal.

Technique

A carefully obtained history and physical examination should be obtained in every patient suspected of anemia because they can provide important clues to an underlying disorder. For investigation of anemia, it is important to ask certain questions in addition to those conveniently explored during a routine periodic examination. Areas of inquiry that we have found valuable are briefly discussed below.

History

The duration of anemia can often be established by obtaining a history of previous blood examination and obtaining those records. Similarly, a history of rejection as a blood donor or prior prescription of hematemics may provide clues that the anemia was previously detected. A careful family history should be obtained not only for anemia but also for jaundice, cholelithiasis, splenectomy, bleeding disorders, and abnormal hemoglobins. The patient's occupation, hobbies, prior medical treatment, drugs, and household exposures to potentially noxious agents should be carefully queried. Patients will not volunteer exposure to tranquilizers, aspirin, insecticides, paints, solvents, or hair dyes unless specifically asked.

In searching for blood loss, a careful documentation of pregnancies, abortions, and menstrual loss must be undertaken. Estimates of menstrual loss are notoriously inaccurate if only routine inquiry is made. Female patients will report that their menses are normal unless there has been a change in the quantity of blood loss; normal menses may vary from 10 ml to 250 ml per period. Therefore it becomes important to attempt to quantify the number of tampons and pads utilized monthly. The significance of black stools is often not appreciated by patients, and changes in bowel habits can be useful in uncovering neoplasms of the colon, steatorrhea, and even achlorhydria; each of which can be associated with anemia. Hemorrhoidal loss is difficult to quantify and may be either disregarded or overestimated from one patient to another. Obviously, a careful history of gastrointestinal complaints that might suggest gastritis, peptic ulcer, hiatal hernia, or diverticuli should be sought. An abnormal color of urine can occur in renal and hepatic disease as well as with hemolytic anemia.

A detailed dietary history is important in the anemic patient and must include not only what foods the patient eats or avoids but also some estimate of their quantity. A meal-by-meal description is necessary to obtain appropriate estimates; even then, patients will frequently attempt to mislead the physician because of embarrassment regarding dietary idiosyncrasies or financial restrictions. In these circumstances, a close and concerned family member's participating in the description of the diet can often be helpful. Patients must be specifically questioned regarding their consumption of either clay or laundry starch because this history will not be provided spontaneously. Changes in body weight are important, not only with regard to dietary intake, but because they can suggest the presence of malabsorption or an underlying wasting disease of infectious, metabolic, or neoplastic origin.

Nutritional deficiencies may be associated with certain unusual symptoms. Iron deficient patients frequently chew or suck ice. Occasionally they complain of dysphagia, brittle fingernails, impotence, fatigue, and cramps in the calves on climbing stairs that are out of proportion to the severity of the anemia. In vitamin B_{12} deficiency, early graying of the hair, a burning sensation of the tongue, and loss of proprioception are common.

A loss of proprioception should be suspected if the patient stumbles in the dark or must look in order to put on either pants or shoes. Paresthesias or unusual sensations that are frequently described as pain also occur in pernicious anemia. Folate deficient patients may have a sore tongue, cheilosis, and symptoms associated with steatorrhea. The color, bulk, frequency, and odor of stools, as well as whether the feces float or sink, can be helpful in suspecting malabsorption.

The history or presence of fever should be obtained

because infections, neoplasms, and collagen vascular disease can be a cause of anemia. Similarly, the occurrence of purpura, ecchymoses, and petechiae suggest either thrombocytopenia or some other bleeding disorders that may be an indication that more than one bone marrow element is affected or that a coagulopathy is a cause of the anemia because of bleeding.

Cold intolerance can be an important symptom of hypothyroidism, lupus erythematosus, paroxysmal cold hemoglobinuria, and certain of the macroglobulinemias. The relation of dark urine to physical activity or time of day can be important in march hemoglobinuria and paroxysmal nocturnal hemoglobinuria.

Last, the presence or absence of symptoms suggesting an underlying disease such as cardiac, hepatic, and renal disease, chronic infection, and endocrinopathy or malignancy should be sought.

Physical Examination

Too often the physician rushes into the physical examination without looking at the patient to ascertain if there is an unusual habitus, an appearance of underdevelopment, malnutrition, or chronic illness, which can be important clues to the underlying etiology of disease. Second, the skin and mucous membranes are often bypassed, so pallor, abnormal pigmentation, icterus, spider nevi, petechiae, purpura, angiomas, ulcerations, palmar erythema, coarseness of hair, puffiness of the face, thinning of the lateral aspects of the eyebrows, nail defects, and an unusual prominent venous pattern on the abdominal wall are missed in the rush to examine the heart and lungs. Optic fundi should be carefully examined, but not at the expense of the conjunctiva and sclera, which can show pallor, icterus, splinter hemorrhages, petechiae, comma signs in the conjunctival vessels, or telangiectasia that can be helpful in planning additional studies. A systemic examination for palpable enlargement of the lymph nodes must be made for evidence of infection or neoplasia. Bilateral edema is useful in disclosing underlying cardiac, renal, or hepatic disease, whereas unilateral edema may portend lymphatic obstruction due to a malignancy that cannot be seen or palpated. A careful search for both hepatomegaly and splenomegaly should be undertaken. Not only is their presence or absence important but also the size of the kidneys and liver, tenderness, firmness, and the presence or absence of nodules. In chronic disorders, these organs are firm and nontender, whereas with carcinoma they may be hard and nodular. The patient with an acute infection usually has a palpably softer and more tender organ.

A rectal and pelvic examination cannot be neglected because tumor or infection of these organs can be the cause of anemia. The neurologic examination should include tests of position and vibratory sense as well as examination of the cranial nerves and testing for tendon reflexes. Obviously, the heart size cannot be ignored because enlargement may provide evidence of the duration and severity of the anemia, and murmurs may be the first evidence of bacterial endocarditis that could explain the etiology of the anemia.

Laboratory Planning

If an adequate history and physical examination have been performed, the etiology of anemia may be obvious and confirmatory studies and appropriate therapy undertaken with a minimum of investigation. If this is not the case, a definite plan of investigation must be initiated. This should consider the cost to the patient, as well as establishing the etiology of the abnormality. A rational approach is to begin by examination of the peripheral smear and the laboratory values obtained on the blood count. If the anemia is either microcytic or macrocytic or if certain abnormal red blood cells or white cells are seen in the peripheral smear, the investigative approach can be limited (see Tables 147.1–3). For example, in a microcytic hypochromic anemia, a source of bleeding should be sought; the appropriate laboratory tests would be either a serum iron and total iron binding capacity, a serum ferritin value, or a stain of a bone marrow specimen for iron. If the serum iron was decreased and the total iron binding capacity increased, a diagnosis of iron deficiency could be made, therapy initiated, and a search for the cause of the iron deficiency begun. If this cannot be shown, then each of the other causes of a microcytic anemia listed in Table 147.1 should be suspected; the order in which they should be investigated could be influenced by findings in the history, physical examination, and peripheral smear. Similarly, with a macrocytic anemia, a reasonable approach would be to determine if the bone marrow aspirate was megaloblastic and if so, attempt by appropriate laboratory studies to incriminate either vitamin B_{12} or folic acid deficiency. Similar to the establishment of a diagnosis of iron deficiency anemia, a diagnosis of vitamin B_{12} or folic acid deficiency does not stop with an abnormal laboratory value for one of these vitamins because the underlying etiology must be delineated.

If a normocytic, normochromic anemia is encountered, steps that should be taken include categorization of the anemia into the three possible etiologies: blood loss, hemolysis, or decreased production. The history and appropriate physical examination with the search for occult blood in the stool, together with an evaluation of the status of iron stores, will be helpful in excluding blood loss as a cause. Hemolysis can be detected in anemic patients by the presence of indirect bilirubinemia and/or reticulocytosis. If the first two etiologies can be excluded with reasonable probability, a bone marrow biopsy should be obtained to search for causes of decreased red cell production. Once the appropriate category has been established, the sequence of investigation to delineate the etiology becomes obvious and should be pursued as outlined below. Utilizing these approaches to the diagnosis of anemia, the clinician will usually discover the etiology.

Basic Science and Clinical Significance

There are only three causes of anemia: blood loss, increased blood destruction, and decreased blood production. In most anemias, one of these causes is the dominant factor. In certain anemias, however, more than a single cause may occur. For example, pernicious anemia is predominantly due to decreased production of erythrocytes, but hemolysis adds to the severity of anemia. In many patients the etiology of the anemia is apparent, and an organized search for the cause is not needed. Examples are patients with known gastrointestinal hemorrhage or the cancer patient undergoing intensive chemotherapy. Similarly, if the anemia is either microcytic or macrocytic or is associated with peculiar abnormalities of the shape of the red blood cell, the etiology

Table 147.1
Microcytic Hypochromic Anemia

	Serum iron	TIBC[a]	Serum ferritin	Bone marrow iron	Comment
Iron deficiency anemia	↓	↑	↓	0	Responds to iron therapy
Anemia of chronic disorders	↓	↓	↑	+ +	Unresponsive to iron therapy
β-Thalassemia major	↑	N	↑	+ + + +	Indirect bilirubinemia and reticulocytosis
β-Thalassemia minor	N	N	N	+ +	Elevation of A_2 or fetal hemoglobin
α-Thalassemia	N	N	N	+ +	
Hemoglobin H disease	N ↑	N	N ↑	+ + +	
Hemoglobin C & E disease	N	N	N	+ +	
Lead intoxication	N	N	N	+ +	
Sideroblastic anemias	↑	N	↑	+ + + +	Ring sideroblasts in marrow

[a]TIBC = total iron binding capacity.

Table 147.2
Macrocytic Anemia

Megaloblastic bone marrow
- Deficiency of vitamin B_{12}
- Deficiency of folic acid
- Drugs affecting DNA synthesis
- Inherited disorders of DNA synthesis
- Erythroleukemia

Nonmegaloblastic bone marrow
- Liver disease
- Hypoplastic and aplastic anemia
- Myelophthisic anemias
- Hypothyroidism and hypopituitarism
- Accelerated erythropoiesis (reticulocytosis)

Table 147.3
Various Forms of Red Blood Cells

Macrocyte: Larger than normal (>8.5 μm diameter) (see Table 147.2)
Microcyte: Smaller than normal (<7 μm diameter). Often hypochromic (see Table 147.1)
Hypochromic: Less hemoglobin in cell. Enlarged area of central pallor (see Table 147.1)
Spherocyte: Loss of central pallor, stains more densely, often microcytic. Hereditary spherocytosis and certain acquired hemolytic anemias
Target cell: Hypochromic with central "target" of hemoglobin. Liver disease, thalassemia, hemoglobin D. Postsplenectomy
Leptocyte: Thin hypochromic cell with a normal diameter and decreased MCV. Thalassemia
Elliptocyte: Oval to cigar shaped. Hereditary elliptocytosis, certain anemias particularly B_{12} and folate deficiency
Schistocyte: Fragmented helmet-shaped or triangular red blood cell. Microangiopathic anemias, artificial heart valves, uremia, malignant hypertension
Stomatocyte: Slit-like area of central pallor in erythrocyte. Liver disease, acute alcoholism, malignancies, hereditary stomatocytosis, and artifact
Tear-shaped RBC: Drop-shaped erythrocyte, often microcytic. Myelofibrosis and infiltration of marrow with tumor, thalassemia
Acanthocyte: Five to 10 spicules of various lengths and at irregular intervals on surface of red cell
Echinocyte: Evenly distributed spicules on surface of red cell, usually 10 to 30. Uremia, peptic ulcer, gastric carcinoma, pyruvic kinase deficiency, preparative artifact
Sickle cell: Elongated cell with pointed ends. Hemoglobin S and certain types of hemoglobin C and I

can be pursued as outlined above. In the majority of patients, however, the cause is not obvious, and an organized and intelligent search must be undertaken. This can be best accomplished by determining which of the three causes cited above is operative in producing the anemia.

Blood Loss

Obviously, significant hemorrhage will produce anemia. Immediately after blood loss, the hematocrit cannot be used as a method to determine the quantity of blood lost because the patient loses plasma with red blood cells. After acute hemorrhage, the hematocrit will fall for several days until the plasma volume is replaced. At that time, the anemia will have normocellular indices because most of the cells in the peripheral blood will have been produced prior to bleeding. If hemorrhage is sufficient to deplete iron stores (1 to 2 liters of blood, 500 to 1000 mg of iron), newly formed erythrocytes will be microcytic and hypochromic, and gradually replace the normal erythrocytes remaining in the circulation. The red cell indices will not become abnormal for 2 or 3 months after bleeding.

Hemorrhage from most body organs is noticed by the patient. Epistaxis, hemoptysis, or hematuria of sufficient degree to cause anemia is usually reported to the physician long before iron deficiency ensues. However, bleeding from the gynecologic organs or the gastrointestinal tract may be disregarded by the patient or go totally undetected until the anemia becomes profound and symptomatic. Menstrual bleeding is variable among normal females and may vary from 10 ml to 250 ml monthly (5 to 125 mg of iron). Unless a change is observed by a patient in menses, the patient relates that her menses are normal, and this may discourage further inquiry. The presence of clots, excessive gushing of blood with the removal of tampons, and the use of an unusual number of pads or tampons with each menses can be used to provide some estimate that menstrual bleeding may be sufficient to produce iron deficiency anemia. Gastrointestinal bleeding is the other occult cause of anemia due to blood loss. If the hemorrhage is profuse, it is usually detected before evidence of iron deficiency anemia occurs. If the bleeding occurs slowly, however, it may remain undetected until anemia ensues. Every patient with iron deficiency anemia should have a stool examination for occult blood. A positive result signifies that a careful search must

be made of the gastrointestinal tract to identify the site of bleeding. Unfortunately, a negative result does not exclude gastrointestinal blood loss because bleeding can be intermittent and because less than 25 ml of blood in the stool per day may go undetected by these means. In this circumstance, detection of radioisotope in stools of patients autotransfused with ^{51}Cr-labeled red blood cells will establish the existence of gastrointestinal bleeding.

The patient's history and physical findings are often useful in detecting the cause of gastrointestinal bleeding. Symptoms suggestive of a hiatal hernia or peptic ulcer quickly lead the clinician to appropriate roentgenographic studies. Evidence of cirrhosis of the liver should lead to a careful search for esophageal varices, gastritis, and hemorrhoids, in addition to performing barium contrast studies of the gastrointestinal tract. Often the sites of gastrointestinal blood loss are less evident, and a thorough search of the bowel by roentgenographic and endoscopic methods must be employed. Even these methods may leave a source of gastrointestinal bleeding undetected because either they will not detect the etiology or the lesion is small. Examples of these include coagulation abnormalities produced by aspirin or by platelet dysfunction, hookworm infestation, hemangiomas of the bowel, lymphosarcoma and other tumors, adenomas of the gallbladder, and the self-administration of anticoagulants.

Increased Blood Destruction

A normal red blood cell survives in the circulation for 120 days. If the erythrocytic life span is shortened significantly, the patient has a hemolytic disorder that may be demonstrated by showing that there is either increased production of erythrocytes or increased destruction or both. The former is most readily shown by the presence of sustained reticulocytosis and the latter by the occurrence of indirect bilirubinemia. Other laboratory tests are available to detect hemolysis, but they are either more expensive or less reliable. Anemia solely due to hemolysis does not occur until red blood cells are being destroyed at six to eight times the normal rate so that the mean red blood cell life span is less than 20 days. Thus, if the clinician relies on the presence of anemia to detect hemolytic states, he will miss the majority. On the contrary, if reticulocytosis and indirect bilirubinemia are used to detect hemolytic states, they will usually be found when the mean life span is less than 50 days. More sophisticated methods, such as measurements of red blood cell life span, are required to detect milder shortening of erythrocyte life span (50 to 100 days) but are only occasionally needed for clinical practice. All patients with both reticulocytosis and indirect bilirubinemia have a hemolytic disorder. All patients with sustained reticulocytosis have a hemolytic disorder. Unfortunately, significant hemolysis can occur without reticulocytosis if the bone marrow is unable to produce red blood cells at an accelerated rate (pernicious anemia, leukemia, aplasia, etc.). Further, a single elevated reticulocyte count is insufficient to establish a diagnosis of hemolysis because transient reticulocytosis may occur without hemolysis, such as in the treatment of iron deficiency anemia. Most patients with indirect bilirubinemia have a hemolytic disorder. In adults, the exception is Gilbert's disease.

Once the presence of hemolysis has been established, the etiology of the increased rate of red blood cells should be sought. All causes of hemolytic disorders are either *hereditary* or *acquired*. Similarly, they are either due to an intrinsic abnormality of the red blood cell (intracorpuscular defect) or caused by extrinsic causes that shorten the erythrocyte life span (extracorpuscular) (Table 147.4).

Hereditary etiologies of hemolytic disease should be suspected in any patient with a family history of anemia, jaundice, cholelithiasis, or splenectomy. Whenever possible, blood relatives should have a hematologic examination (hemoglobin concentration, reticulocyte count, indirect bilirubin determination, and a careful examination of the peripheral smear). Establishment of a hemolytic defect in blood relatives permits a presumptive diagnosis of a hereditary intra-

Table 147.4
Classification of the Hemolytic Disorders

Hereditary	Acquired
Intracorpuscular Defect	
Disorders of the RBC membrane and cytoskeleton (hered. spherocytosis, elliptocytosis, pyropoikilocytosis)	
Abnormalities of hemoglobin and hemoglobin synthesis (hemoglobinopathies, thalassemia)	
Congenital dyserythropoietic anemias	
Hereditary RBC enzymatic defects (G6PD, pyruvate kinase, etc.)	B_{12} or folate deficiency
	Severe iron deficiency
	Paroxysmal nocturnal hemoglobinuria
Extracorpuscular Defect	
	Physical agents (burns, cold exposure)
	Trauma (prosthetic heart valves, DIC)
	Infectious agents (malaria, toxoplasmosis, mononucleosis, hepatitis, mycoplasma, clostridia, bartonella, leishmaniasis)
	Hepatic and renal disease
	Collagen vascular diseases
	Neoplasia (leukemia, lymphoma, Hodgkin's disease)
	Transfusion of incompatible blood
	Hemolytic disease of newborn
	Cold hemagglutinin disease
	Idiopathic autoimmune hemolytic anemia (warm antibodies)

vascular hemolytic disorder in the patient. Once the probability of a hereditary hemolytic disorder has been established, a planned approach to establish a definitive abnormality is usually simple. A careful examination of the peripheral smear may provide important clues (spherocytes, ovalocytes, sickle cells, target cells, etc.). Other laboratory studies in hereditary hemolytic disorders include incubated osmotic fragility studies (spherocytes), hemoglobin electrophoresis (hemoglobinopathies), isopropanol or heat denaturation tests (unstable hemoglobins), oxygen dissociation curves (abnormal oxygen affinity hemoglobins), A_2 and fetal hemoglobin determination (beta thalassemia), and specific red blood cell enzyme assays for evidence of an enzymatic deficiency of the aerobic or anaerobic glycolytic pathways (glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency, etc).

The age at which the hemolytic disorder is detected is not always helpful in determining that it is hereditary. Congenital manifestations are often unusual; infants with sickle cell disease or beta thalassemia appear normal at birth, most patients with G6PD deficiency have no manifestation of their erythrocyte enzymatic abnormality until they receive an oxidant drug, and thalassemia minor is usually not detected until a routine hemogram is performed and then it is often mistaken for iron deficiency anemia because of the microcytosis and hypochromia.

Acquired hemolytic disorders occur in a large number of diseases and vary considerably in severity. In addition, hemolysis may be observed as a result of physical injury to the red blood cell or following exposure to drugs, chemicals, or venoms. In many patients, the etiology of the hemolytic disorder is apparent because of other manifestations of the disease (cirrhosis, severe renal insufficiency, hematologic malignancies, burns, cold exposure, etc). In others, it can be an important clue to the underlying disorder (infections, collagen vascular disease, etc). A positive antiglobulin (Coombs) test can be extremely helpful. It not only provides evidence that the hemolytic disorder is an acquired extracorpuscular defect but limits it to the group of disorders associated with autoimmune hemolytic anemia, which includes: (1) drug-dependent antibodies (penicillin, quinidine, alpha methyldopa, etc.); (2) coexistence of an underlying disease (hematologic malignancies, lupus erythematosus, certain viral infections); and (3) idiopathic groups in which an underlying disease cannot be demonstrated.

Usually the acquired hemolytic disorders with an intracorpuscular defect are not difficult to diagnose. Vitamin B_{12} and folic acid deficiency are associated with a macrocytic anemia, hypersegmented polymorphonuclear leukocytes in the peripheral smear, a megaloblastic bone marrow, physical findings of the underlying deficiency state, and abnormal serum and red cell levels for the deficient vitamin. Iron deficiency in the United States is rarely of sufficient severity to cause significant hemolysis and is mentioned here for the sake of completeness. Paroxysmal nocturnal hemoglobinuria will be diagnosed only if the physician considers it when there is pancytopenia or hemoglobinuria. Exclusion of this cause of hemolysis can usually be accomplished by the performance of a sugar water test and, if this is positive, by a confirmatory acid hemolysis test (Ham test).

The major diagnostic problem encountered with the hemolytic disorders occurs when the known causes for hemolysis have been excluded by history, physical examination, and laboratory studies, the Coombs test is negative, and insufficient family members can be tested to differentiate between the hereditary intracorpuscular hemolytic disorders and the acquired extracorpuscular defects. A donor cell ^{51}Cr red blood cell survival study can provide this differentiation. Labeled red blood cells from a normal blood donor of a compatible blood group will have a normal survival in patients with hereditary hemolytic disease and a shortened life span in those with an acquired extracorpuscular defect. This differentiation can be important in determining prognosis and selecting appropriate therapy.

Decreased Blood Production

A diminished production of red cells should be suspected in all patients without evidence of either blood loss or hemolysis. Thus the anemia patient without evidence of bleeding or iron deficiency who has a normal indirect bilirubin and a normal or decreased reticulocyte count most probably has a defect in the production of erythrocytes. Many of these patients have pancytopenia or abnormalities of the leukocytes or platelets detected by examination of a peripheral smear. When this group of disorders is suspected, the most important laboratory test is a bone marrow biopsy and aspirate. The bone marrow biopsy will permit categorization of these disorders into three separate groups: (1) aplasia or hypoplasia, (2) hyperplasia, and (3) bone marrow replaced with nonhematopoietic elements (Table 147.5).

The aplastic and hypoplastic disorders are commonly caused by drugs and chemicals. Certain of these causative agents are dosage related, whereas others are idiosyncratic. Any human exposed to a sufficient dose of inorganic arsenic, benzene, radiation, or the usual chemotherapeutic agents employed for the treatment of neoplastic disease will develop bone marrow depression with pancytopenia. The idiosyncratic agents produce suppression of one or more of the formed elements of the bone marrow in a small percentage of exposed people. With certain of these drugs, pancytopenia is more common, whereas with others, suppression of one cell line is usually observed. Other idio-

Table 147.5
Decreased Production of Red Blood Cells

Aplastic or hypoplastic bone marrow
Drugs, chemicals & related causes:
Dosage related: Heavy metals, benzene, radiation, antineoplastic drugs, chloramphenicol
Idiosyncratic: Antibiotic, antibacterial, anticonvulsant, antidiabetic, antithyroid, antihistamine, anti-inflammatory, anti-insecticide, antiarthritic, antidepressant medications
Other acquired etiologies: Viral hepatitis, paroxysmal nocturnal hemoglobinuria
Familial: Fanconi syndrome, constitutional erythroid hypoplasia
Hyperplastic bone marrow
Deficiency states: B_{12}, folate or iron deficiency
Drugs inhibiting DNA synthesis
Inborn errors of metabolism
Erythroleukemia
Idiopathic
Infiltration of bone marrow
Myelofibrosis
Neoplasia
Infection—tuberculosis & fungal infections
Metabolic abnormalities: Gaucher's disease, amyloid, mastocytosis, marble bone disease

syncratic causes of aplasia are viral hepatitis and paroxysmal nocturnal hemoglobinuria. A definite etiology cannot be established in half of aplastic patients and then the disorder must be classified as *idiopathic*. Whenever possible, a cause for the aplastic anemia should be sought because cessation of exposure may lead to recovery. Rarer causes of anemia due to a hypoplastic bone marrow include familial disorders and the acquired pure red cell aplasias. The latter is characterized by a virtual absence of erythroid precursors in the bone marrow with normal numbers of granulocytic precursors and megakaryocytes.

In patients with a hyperplastic bone marrow and decreased production of red blood cells, there is a group with an excellent prognosis and an unresponsive group refractory to therapy with a relatively poor prognosis. The former includes disorders of relative bone marrow failure due to nutritional deficiency in which proper treatment with either vitamin B_{12}, folic acid, or iron leads to correction of the anemia once the appropriate etiology is established. Drugs that act as antifolic antagonists or inhibit DNA synthesis can produce similar effects. The second group includes an idiopathic hyperplasia that may partially respond to pyridoxine therapy in pharmacologic doses but more frequently does not. These patients frequently have ring sideroblasts in the bone marrow indicating that there is an inappropriate utilization of iron in the mitochondria. Certain of these patients may have refractory anemia for years, and some eventually develop acute leukemia. Rare causes of diminished erythrocyte production with hyperplastic bone marrow include hereditary orotic aminoaciduria and erythremic myelosis.

Last, infiltration of the bone marrow with fibrous tissue, neoplastic cells, or other cells that replace normal hematopoietic tissue can diminish the production of red blood cells, granulocytes, and platelets. A diagnosis of myelofibrosis or neoplastic involvement of the bone marrow can often be suspected by evidence of myeloid metaplasia in the peripheral smear. Replacement of the bone marrow with nonhematopoietic cells leads to activation of fetal sites of blood production in organs such as the liver and the spleen with release of abnormally shaped erythrocytes and normoblasts, immature granulocytes, and large platelets into the peripheral blood. Myeloid metaplasia does not occur in aplastic disease. Thus its presence in an anemic patient should lead to a suspicion of bone marrow infiltration even before the biopsy specimen is obtained.

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